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Please find below and/or attached an Office communication concerning this application or proceeding.

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/674,962
Filing Date: November 08, 2000
Appellant(s): HAUER ET AL.

S. Peter Konzell
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/11/08 appealing
from the Office action mailed 2/27/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

A decision on the above-identified application was made by the Board April 28, 2006 (Appeal No: 2005-2596).

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

This appeal involves claims 5-9.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(8) Evidence Relied Upon

5,846,821	Guerinot et al	12-1998
EP 406,814	Haymore et al	07-1990

Volz, J. "Molecular characterization of metal-binding polypeptide domains by electrospray ionization mass spectrometry and metal chelate affinity chromatography", Journal of Chromatography, vol. 800 (1998), pp. 29-37.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Volz et al in view of Guerinot et al and Haymore et al.

Volz et al disclose at page 32, col. 2, a peptide fragment of the formula HxHxxxCxxC. A species of this generic peptide fragment is disclosed at page 34, Fig. 2, compound (a). Volz further discloses at page 29, col. 1 that a number of peptides and proteins containing certain **motifs of histidine and cysteine residues are known** to specifically bind divalent transition

metal ions. **Typical binding sites for Cu²⁺, Zn²⁺ and Ni²⁺ ions comprise CxxC motifs.** Volz also discloses that the metal binding property of the peptide fragment reside in the presence of the two His and Cys residues.

Guerinot discloses at col. 14, line 27 conservative amino acid residues substitution e.g., Leu with Ile in the non-critical positions of a peptide sequence.

Haymore, like Guerinot, discloses at page 4, line 12 peptide fragments that are metal binding peptides where the nature of the intervening residues is relatively unimportant. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to pick and choose from the 20 naturally occurring amino acid, the ones that can occupy the x positions(non-critical residues) in the peptide sequence (Cys-His) motif of Volz. Haymore, Guerinot and Volz all disclose that amino acids at the noncritical or intervening residues between the His and Cys metal binding residues are relatively unimportant in the binding of peptide fragments to metals. One would reasonably expect successful binding of the peptide fragments to metal ions since all of the prior art teaches the metal binding residues in the critical His and Cys residues of the motif. The Board concurred in their decision in the above-identified application.

Volz positively teaches the essential or critical residues for metal ion binding are the His and Cys residues. In this regard, we find that Volz refers to the different metal ion binding regions as "motifs." For example, Volz describes the correspondent peptide as containing a H-X-H-X-X-C-X-X-C motif. See, e.g., the abstract. Thus, Volz suggests, and Haymore confirms (p. 4, lines 10-13), that the intervening amino acids denominated as "X" are not critical to the metal binding activity of the peptide. In addition, Haymore states that the intervening residues are not important. Accordingly, the teachings of Volz and Haymore would have suggested that any naturally-occurring amino acid could be used in the H-X-H-X-X-C-X-X-C motif. This would include the amino acids recited in claims 5 and 6.

(10) Response to Argument

Applicants assert that none of the pending claims recite peptides containing Ile in X3 position.

In reply, claim 9, Seq. ID. 5 contains Ile, albeit, at position X1. However the combined teachings of the art has already shown that whether Ile is at the X1 or X3 position or at any one of positions of the X1-X6 the metal binding property of the peptide is retained. Thus, provided the essential binding

residues His and Cys are present in the peptide motif taught by Volz, the peptide would exhibit metal binding property. Volz teaches that any of the 20 naturally-occurring amino acid residues can be in the XI-X6 positions. Guerinot and Haymore concurred with Volz's teachings. Guerinot showed that replacement of residue i.e., Leu with Ile did not affect the metal binding property of the peptide.

Applicants assert that the claims provide novel peptide fragments that exhibit increased protein selectivity and simplification of protein purification when compared with known fragments. (Specification page 3, lines 1-7).

In reply, a review of the cited section (page 3, lines 1-7) does not reveal any of the specific sequences of claims 6-9, especially the subgenus of claim 5. Rather, a generic scope containing various residues from the 20 naturally occurring residues at different X1-X6 positions. (Note the presently claimed subgenus sequence does not contain the His and Cys residues. The subgenus has been carved out from the as-filed genus where His and Cys residues in the motif has been deleted). More importantly, the cited section does not disclose that the specific claimed sequences of claims 6-9, especially the subgenus of claim 5; exhibit e.g., **increased** protein selectivity. Cf. with the results at e.g., Table 1, page 19 of

Art Unit: 1633

the instant specification. The Table discloses that sequences Seq. ID. NOs. 2-5 have only **good** (not increased) binding activity. Furthermore, the claims recite peptides **comprising** of the amino acid sequence as claimed. In using the word comprising the other amino acids present in the peptide of Volz are not precluded. The claimed peptide thus has similar, if not the same, binding affinity as that of the prior art. No new and unexpected results over the prior art peptide has been demonstrated by the present claimed peptide. It would be within the ordinary skill in the art to determine which sequences from the known ones are better binders as taught by Volz.

Volz discloses at page 37, col. 1, paragraph 5:

ESI-MS and metal chelate affinity chromatography revealed **different metal ion selectivity** of these peptide sequences. As general motifs for Ni²⁺ ion binding, sequences were identified which contain two or more histidine residues in close proximity i.e. HxH and HxxH. Cysteine-containing motifs such as CxxC were capable to bind Cu²⁺ but not Ni²⁺ ions. Ni-NTA chromatography was used to effectively purify ATPase- 439, and Cu-NTA chromatography to separate APP from non-metal-binding proteins. Since the isolation of the native APP-protein has been found difficult so far, the observed metal ion specificity may lead to an improved purification procedure. Furthermore, the present study demonstrates the possibility of protein purification from metal chelate chromatography without using an additional oligo- histidine (His-tag) sequence, indicating the **efficient NTA chromatographic purification of proteins having suitable natural binding motifs**. (Emphasis supplied).

The findings of Volz that some sequences preferentially bind one metal from the other are confirmed by no less than appellants' experiments, Example 6 (page 19) performed by the inventors. In these experiments, claimed SEQ ID NOs. 2, 3, 4 and 5 **bind well** to the nickel metal chelate column, whereas other tested variations on the HxHxxxCxxC formula, **show no binding**. Specifically, SEQ ID NO:3 produced a protein yield of 56%, which is higher than the 48% with the his tags. SEQ ID NO:3 also showed preferred binding to Ni²⁺ and Cu²⁺, while no binding to Zn²⁺ was observed. "On use of Ni chelate columns, the clone MI3 [corresponding to SEQ ID NO:3] showed distinctly better purification of the proteins by comparison with the his tags. Conversely, the latter resulted in a purer product by comparison with MI3 on use of Cu chelate columns." (Specification page 20, lines 29- 35.)

Accordingly, as stated by the Board, the teachings of Volz and Haymore would have suggested that any naturally-occurring amino acid could be used in the H-X-H-X-X-X-C-X-X-C motif. [This would include the amino acids recited in claims 5-9].

Appellant submits that the X positions are essential in such positions which support the non-obviousness of the instant claims. Appellant submits that Guerinot et al. specifically states that, "conservative amino acid substitution" is one in

which the amino acid residue is replaced with an amino acid residue having a similar side chain." (column 14, lines 18-21) (Emphasis added). Accordingly, Guerinot et al. defines families of amino acid residues having similar side chains; wherein the family of "non-polar" side chain amino acids is defined to include alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, and tryptophan. (column 14, lines 21-30) (Emphasis added). Additionally, Guerinot et al. concludes "a predicted nonessential amino acid residue...is preferably replaced with another amino acid residue from the same side chain. (column 14, lines 30-33). Consequently, contrary to the Examiner's assertion, there is simply no teaching or suggestion to substitute an amino acid of one side chain family with an amino acid from another side chain family or to simply pick and choose from among the 20 naturally occurring amino acids for each of positions X1-X6. "The fact that a claimed species is or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a prima facie case of obviousness." In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." Id., citing In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). "A disclosure of millions of compounds does

not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the invention." Id.

In reply, as recognized by appellant, Guerinot teaches conservative amino acid substitution and defines the residues within or belong to the family of said conservative residues. Thus, if one will pick a polar residue, one would obviously replace it with another polar residue and not with a non-polar residue. One having ordinary skill in the art would therefore know which residues can be conservatively substituted with one another as enumerated by appellants above.

As held by the majority in *Merck & Co. Inc. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 10 USPQ 2d 1843 (Fed. Cir. 1989), at 10 USPQ 2d 1846:

That the '813 patent discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the **identical purpose** taught by the prior art. See *In re Corkill*, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed. Cir. 1985) (obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among "thousands of compounds"); *In re Susi*, 440 F.2d 442, 445, 169 USPQ 423, 425 (CCPA 1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellants generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives"). (Emphasis added).

When a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.

- When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one.
-
- If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability.
KSR v. Teleflex, 17 S. Ct. 1727, 82 USPQ 2d 1385 (2007).

Appellants submit while the Board of Patent Appeals & Interferences Decision stated that, "the only difference between the prior art peptide fragment and the [claimed] peptide fragment...is a Ile residue at position X3 instead of a Leu residue, we agree with the [E]xaminer that it would have been obvious to one of ordinary skill in the art to construct a peptide fragment having the claimed conservative amino acid substitution (i.e., a peptide fragment wherein X3 is a Leu residue)," (page 5, lines 16-18) and further indicated that Guerinot et al., "merely provides evidence of the correctness of the Examiner's position that these two amino acids are functional equivalents," referring to Ile and Leu (page 6, lines 14-15), Appellant respectfully submits that claims 5-9 were amended subsequent to the Decision such that they do not recite

"non-polar" side chain amino acids, such as Ile, for position X3. Rather, Appellant respectfully submits that claims 5-9 recite that position X3 comprises one of "uncharged polar" side chain amino acids glycine, threonine, and tyrosine. At least according to Guerinot et al., amino acids in "non-polar" and "uncharged polar" families are not regarded as conservative substitutions. (column 14, lines 18-30).

In reply, the Board in their decision also stated that:

Upon return of the application to the corps, the examiner may wish to reconsider whether claims 5 and 6 are patentable over the teachings of the applied prior art. We point out that in the Answer (page 9), the examiner argues that "Volz positively teaches the essential or critical residues for metal ion binding are the His and Cys residues." In this regard, we find that Volz refers to the different metal ion binding regions as "motifs." For example, Volz describes the correspondent peptide as containing a H-X-H-X-X-X-C-X-X-C motif. See, e.g., the abstract. Thus, **Volz suggests, and Haymore confirms (p. 4, lines 10-13), that the intervening amino acids denominated as "X" are not critical to the metal binding activity of the peptide. In addition, Haymore states that the intervening residues are not important.** Therefore, the examiner should consider whether the teachings of Volz and Haymore would have suggested that any naturally-occurring amino acid could be used in the H-X-H-X-X-X-C-X-X-C motif. This would include the amino acids recited in claims 5 and 6. (Emphasis added).

As stated above, and as recognized by appellants, Guerinot teaches conservative substitution among the family of residues e.g., polar residues for polar ones and non-polar for non-polar residues. One having ordinary skill in the art would know to

substitute only members that belong to the same family.

Guerinot's teaching combined with the teachings of Volz that any of the 20 naturally occurring residues could occupy the X positions would lead one having ordinary skill in the art to the claimed peptide. One having ordinary skill in the art would have reasonably expected that replacement of one naturally occurring amino acid with another will result in a metal binding peptide provided Cys and His residues are present. The metal binding property of the peptide motif as taught by the prior art (and specification) resides in presence of these two critical residues.

Appellants assert that Haymore et al leads one of ordinary skill in the art to conclude the exact opposite, that is, substitution of an intervening amino acid denominated as "X" would result in no change in the metal binding activity of the peptide. Appellant respectfully submits that the prior art, thus, actually suggests that any attempt to substitute an intervening amino acid denominated by "X" would yield no material effect metal binding properties and would be futile in nature.

In reply, if there is no change in the metal binding activity of the peptide, it does not mean that the peptide has no binding activity. Rather, that the peptide binding

activity/selectivity remains the same i.e., neither increases nor decreases its binding effect. The fact that Haymore teaches occurrence of binding suffice the finding of obviousness of the claimed peptide. Cf. with Example 6, page 19 of the instant specification as stated above. Also, the claimed "comprising" language does not preclude the amino acids present in the peptide motif of Volz. Therefore, the peptide of Volz exhibits similar, if not the same, binding selectivity as the claimed peptide.

Appellants assert that the Examiner has used hindsight reconstruction and the Appellant's very own disclosure "as a blueprint to reconstruct the claimed invention from the isolated teachings of the prior art," since the "expressed motivation" to make the combination is lacking from the individual references and does not emanate from that knowledge generally available to the skilled artisan. *Grain Processing Corp. v. AmericanA Maize- Prods. Co.*, 840 F.2d 902 (Fed. Cir. 1988).

In response as appellants recognize at page 8, paragraph 4 of the Brief, "[t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and **motivation**, or by overemphasis on the importance of published articles and the explicit content of issued patents[,]" *KSR Int'l v. Teleflex, Inc.*, 550 U.S. __ (2007). Furthermore, it

must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only **knowledge which was within the level of ordinary skill at the time the claimed invention was made**, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). (Emphasis supplied).

The combined teachings of the art would lead one to the claimed metal binding peptide comprising the claimed structure. The prior art teaches that the X residues can be any of the 20 naturally occurring residues. It would be within the ordinary skill in the art at the time the invention was made, given the 20 naturally occurring amino acids, to replace one with another. It is well known in the art that Cys and His are the critical or necessary residues in the peptide motif for binding to occur.

When a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a **predictable result**. Such substitution/replacement is not more than one would not expect or is beyond the skill of one having ordinary skill in the art.

(11) Related Proceeding(s) Appendix

Copies of the Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided by appellants in the instant Brief.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/T. D. Wessendorf/

Primary Examiner, Art Unit 1639

April 21, 2008

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